Ivabradine (CORLANOR)

Criteria for Use

August 2016

VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing. **THE CLINICIAN SHOULD UTILIZE THIS GUIDANCE AND INTERPRET IT IN THE CLINICAL CONTEXT OF THE INDIVIDUAL PATIENT. INDIVIDUAL CASES THAT ARE EXCEPTIONS TO THE EXCLUSION AND INCLUSION CRITERIA SHOULD BE ADJUDICATED AT THE LOCAL FACILITY ACCORDING TO THE POLICY AND PROCEDURES OF ITS P&T COMMITTEE AND PHARMACY SERVICES.**

The Product Information should be consulted for detailed prescribing information. See the VA National PBM-MAP-VPE Monograph on this drug at www.pbm.va.gov or https://vaww.cmopnational.va.gov/cmop/PBM/default.asp for further information.

Exclusion Criteria *If the answer to ANY item below is met, then the patient should NOT receive ivabradine*

- ☐ Acute decompensated heart failure (HF)
- ☐ Recent myocardial infarction (within the past 2 months)
- ☐ Cardiac resynchronization therapy started within past 6 months
- ☐ Atrial fibrillation or atrial flutter
- ☐ Congenital heart disease as etiology of HF
- ☐ Primary severe valvular heart disease as etiology of HF
- ☐ Blood pressure (BP) < 90/50 mm Hg
- ☐ Sick sinus syndrome, sinoatrial block or 2nd (Refer to Monitoring) or 3rd degree AV block, unless a functioning demand pacemaker is present
- ☐ Severe hepatic impairment (Child-Pugh C)
- ☐ Pacemaker with atrial or ventricular pacing (except biventricular pacing) > 40% of the time, or with stimulation threshold at the atrial or ventricular level ≥ 60 bpm
- ☐ Concomitant strong CYP3A4 inhibitors (e.g., azole antifungals, macrolide antibiotics, HIV protease inhibitors, nefazodone) (Refer to Monitoring)
- ☐ Concomitant Class I antiarrhythmic agents (including quinidine, procainamide, lidocaine, phenytoin, mexiletine, etc)
- ☐ Concomitant diltiazem or verapamil (Refer to Monitoring)
- ☐ Family history or congenital long QT syndrome or treated with selected QT-prolonging agents

Inclusion Criteria *The answers to ALL of the following must be fulfilled in order to meet criteria for ivabradine*

- ☐ Restricted to VA Cardiology for initial prescription (Refer to Issues for Consideration)
- ☐ Stable, chronic, symptomatic (New York Heart Association Class II to III) HF (Refer to Issues for Consideration) (must be stable for ≥ 4 weeks in duration)
- ☐ Left ventricular ejection fraction ≤ 35% (Refer to Issues for Consideration)
- ☐ Hospitalization for worsening HF within the past 12 months
- ☐ Normal sinus rhythm with resting HR ≥ 70 bpm (as measured by 12 lead electrocardiogram after ≥ 5 minutes at rest on 2 consecutive visits)
- ☐ Receiving a stable dose (i.e., > 4 weeks) of a beta-blocker (after titration to maximally tolerated target dose as recommended by clinical practice guidelines), or documented intolerance or contraindication to a beta-blocker
- ☐ Receiving a stable dose (i.e., > 4 weeks) of an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB) (after titration to maximally tolerated target dose as recommended by clinical practice guidelines) (Refer to Issues for Consideration), or documented intolerance or contraindication to an ACEI or ARB
- ☐ Receiving a stable dose (i.e., ≥ 4 weeks) of a mineralocorticoid receptor antagonist (MRA) (after titration to maximally tolerated target dose as recommended by clinical practice guidelines) (Refer to Issues for Consideration), or documented intolerance or contraindication to a mineralocorticoid receptor antagonist

For women of childbearing potential

- ☐ use of effective contraception, and provided education on the potential risk vs. benefit of taking ivabradine if patient were to become pregnant

Dosage and Administration

- The recommended starting dose of ivabradine is 5 mg twice daily, with meals. Ivabradine should be started at 2.5 mg twice daily in patients with conduction defects or in whom bradycardia could lead to hemodynamic compromise.
- After 2 weeks, the patient should be assessed, with dose adjustments based on heart rate (per below):

Heart Rate*	Dose Adjustment
> 60 bpm	Increase by 2.5 mg (given twice daily), up to a maximum dose of 7.5 mg twice daily
50 to 60 bpm	No change in dose
< 50 bpm or signs & symptoms of bradycardia	Decrease by 2.5 mg (given twice daily); if the current dose is 2.5 mg twice daily, discontinue therapy

*Note that beta-blocker dose should not be reduced only to allow for initiation or titration of ivabradine

Monitoring

- **Fetal Toxicity:** Based on animal studies, ivabradine may cause fetal toxicity if administered to pregnant women. Females should be advised to use effective contraception when taking ivabradine.
- **Atrial fibrillation** is increased with ivabradine (9%; vs. 8% placebo per SHIFT); it is recommended to regularly monitor cardiac rhythm, and to discontinue ivabradine if atrial fibrillation occurs.
- **Bradycardia, sinus arrest, and heart block** have occurred with ivabradine. Risk factors for bradycardia include: sinus node dysfunction, conduction defects (e.g., 1st or 2nd degree AV block, bundle branch block), ventricular dyssynchrony, use of other negative chronotropes (e.g., digoxin, diltiazem, verapamil, amiodarone). It is noted that diltiazem or verapamil may result in lowering of HR, as well as increase exposure to ivabradine with concomitant use; therefore, use of these medications with ivabradine should be avoided. It is recommended that ivabradine be avoided in patients with 2nd degree AV block unless a functioning demand pacemaker is present.
- **Phosphenes** or luminous phenomena has been reported in 3% on ivabradine; symptoms reported as mild to moderate intensity, with < 1% of patients discontinuing therapy, and most resolving during or after treatment.
- **Drug Interactions**
  - **Cytochrome P450 interactions:** ivabradine is primarily metabolized by CYP3A4; therefore, concomitant use of strong CYP3A4 inhibitors including azole antifungals (e.g., itraconazole, ketoconazole), macrolide antibiotics (e.g., clarithromycin, telithromycin), HIV protease inhibitors (e.g., nelfinavir), and nefazodone are contraindicated due to the potential for increased plasma concentrations of ivabradine that may result in exacerbation of bradycardia and conduction disturbances. Concomitant use of moderate CYP3A4 inhibitors (e.g., diltiazem, verapamil, grapefruit juice), or CYP3A4 inducers (e.g., St. John's wort, rifampicin, barbiturates, phenytoin) should be avoided.
  - **Negative chronotropes:** the majority of patients treated with ivabradine will also be receiving treatment with a beta-blocker. There is an increased risk for bradycardia in patients who are receiving medications that also slow HR (e.g., amiodarone, beta-blockers, digoxin). Heart rate should be monitored in patients receiving ivabradine in addition to other agents that are negative chronotropes.

Issues for Consideration

- **FDA indication:** to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35%, who are in sinus rhythm with resting HR ≥ 70 bpm and are on maximally tolerated doses of beta-blockers or have contraindications to a beta-blocker.
- **Local restrictions:** It is recommended that the patient be evaluated by Cardiology to obtain an initial prescription for ivabradine; if feasible and deemed appropriate. Alternatively, sites may establish a mechanism for patients to be evaluated for an initial prescription by a designated provider(s) (e.g., primary care provider) with appropriate follow-up and titration (e.g., pharmacy titration clinic or follow-up by the PACT pharmacist).
- **New York Heart Association (NYHA) Class II-III HF:** Ivabradine is indicated in patients with stable, symptomatic chronic HF, based on data from a clinical trial (SHIFT) that included patients with primarily NYHA Class II (49%) or III (50%) heart failure.
- **Assessment of LVEF:** It is recommended that LVEF be assessed (e.g., by echocardiography, MUGA, CT scan, MRI, ventricular angiography) within the past 3 months (as per SHIFT) while on optimal, or maximally tolerated, doses of guideline directed medical therapy for heart failure.
- **Optimal therapy for HF**
  - The majority of patients treated in the pivotal outcome trial (SHIFT) with ivabradine were also receiving optimal guideline directed medical therapy; therefore, it is recommended that patients be optimized on an ACEI or ARB, and a MRA, in addition to a beta-blocker, all titrated to optimal doses, as tolerated, prior to considering ivabradine.
  - Sacubitril/valsartan is another therapy for select patients with HF and reduced ejection fraction (VA PBM-MAP-VPE Clinical Guidance Criteria for Use) that demonstrated a reduction in death from cardiovascular causes or HF hospitalization compared to an ACEI. It should be noted that patients treated with sacubitril/valsartan were not included in the SHIFT trial with ivabradine, and place in therapy of sacubitril/valsartan with ivabradine should take into consideration reduction in morbidity and mortality with sacubitril/valsartan, time to determine clinical benefit and tolerability, and lack of safety and efficacy data with concomitant sacubitril/valsartan and ivabradine.

- Although black patients did not represent a large proportion of the population studied in SHIFT, the combination of hydralazine and isosorbide dinitrate was found to reduce mortality and hospitalization and is recommended in African American patients who remain symptomatic despite treatment with an ACEI, beta-blocker and MRA.
- Digoxin may also be considered in patients with persistent symptoms despite guideline directed medical therapy, to reduce HF hospitalizations (DIG Trial). It is noted that only 22% of patients were receiving digoxin at baseline in SHIFT. Although different treatment populations in the trials, given the similar benefit in reducing HF hospitalizations, the place in therapy of digoxin vs. ivabradine should be determined on a case by case basis, taking into consideration patient specific factors, as well as price for the medication.

- **Off-label use**
  - **Coronary artery disease with or without symptomatic HF:** There was no benefit in the primary outcome (cardiovascular mortality and nonfatal myocardial infarction) in a trial (SIGNIFY) of 19,102 patients with coronary artery disease without clinically evident heart failure. Patients with activity-limiting angina (Canadian Cardiovascular Society class II or higher) had a significant increase in the risk for the primary endpoint with ivabradine (7.6%) compared to placebo (6.5%). In another trial (BEAUTIFUL) evaluating 10,917 patients with coronary artery disease, left ventricular ejection fraction < 40%, and resting heart rate $\geq$ 60 bpm, there was no significant difference in the primary composite endpoint (time to first cardiovascular death, hospitalization for acute myocardial infarction, or hospitalization for new-onset or worsening heart failure) with ivabradine compared to placebo.
  - **Tachycardia:** Ivabradine has been found to be effective in reducing symptoms in small short-term studies in patients with inappropriate sinus tachycardia, and in a small retrospective case series of patients with postural orthostatic tachycardia syndrome; use in these patients (off-label) should be determined on a case by case basis.

Discontinuation Criteria

- Patient is not tolerating therapy with ivabradine
- Resting HR < 50 or signs and symptoms of bradycardia despite being on lowest dose (2.5 mg twice daily) ivabradine
- Patient develops atrial fibrillation or atrial flutter

Prepared: July 2015. Contact: Elaine Furmaga, PharmD, VA Pharmacy Benefits Management Services